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Multidisciplinary Center Care for Long COVID Syndrome – a Retrospective Cohort Study

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PII: S0002-9343(23)00328-5
DOI: https://doi.org/10.1016/j.amjmed.2023.05.002
Reference: AJM 17168

To appear in: *The American Journal of Medicine*

Received date: 2 February 2023
Accepted date: 17 May 2023

Please cite this article as: Joseph Bailey M.D. , Bianca Lavelle M.D. , Janet Miller B.S. , Millenia Jimenez B.S. , Patrick H. Lim M.S. , Zachary S. Orban B.S. , Jeffrey R. Clark B.A. , Ria Tomar B.S. , Amy Ludwig M.D. , Sareen T. Ali B.S. , Grace K. Lank B.S. , Allison Zielinski M.D. , Ruben Mylvaganam M.D. , Ravi Kalhan M.D. , Malek El Muayed M.D. , R. Kannan Mutharasan M.D. , Eric M. Liotta M.D. M.S. , Jacob I Sznajder M.D. , Charles Davidson M.D. , Igor J. Koralnik M.D. , Marc A. Sala M.D. , for the Northwestern Medicine Comprehensive COVID Center Investigators, Multidisciplinary Center Care for Long COVID Syndrome – a Retrospective Cohort Study, *The American Journal of Medicine* (2023), doi: https://doi.org/10.1016/j.amjmed.2023.05.002

Multidisciplinary Center Care for Long COVID Syndrome – a Retrospective Cohort Study

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This work is supported, in part, by a generous gift from Mr. and Mrs. Michael Ferro. Dr. Joseph Bailey's work on this project is supported, in part, by NIH/NHLBI 5T32HL076139 and NIH/NHLBI UL1TR001422.
The authors report no conflict of interest.

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Keywords:
Long COVID
Post-Acute Sequelae of SARS-CoV-2 Infection
PASC
Multidisciplinary Care
Health Service Delivery

Structured Abstract

Background: Persistent multi-organ symptoms after COVID-19 have been termed "long COVID" or "post-acute sequelae of SARS-CoV-2 infection" (PASC). The complexity of these clinical manifestations posed challenges early in the pandemic as different ambulatory models formed out of necessity to manage the influx of patients. Little is known about the characteristics and outcomes of patients seeking care at multidisciplinary post-COVID centers.

Methods: We performed a retrospective cohort study of patients evaluated at our multidisciplinary Comprehensive COVID-19 Center (CCC) in Chicago, IL, between May 2020 and February 2022. We analyzed specialty clinic utilization and clinical test results according to severity of acute COVID-19.

Results: We evaluated 1802 patients a median of 8 months from acute COVID-19 onset, including 350 post-hospitalization and 1452 non-hospitalized patients. Patients were seen in 2361 initial visits in 12 specialty clinics, with 1151 (48.8%) in neurology, 591 (25%) in pulmonology, and 284 (12%) in cardiology. Among patients tested, 742/878(85%) reported decreased quality of life, 284/553(51%) had cognitive impairment, 195/434(44.9%) had alteration of lung function, 249/299(83.3%) had abnormal CT chest scans, and 14/116(12.1%) had elevated heart rate on rhythm monitoring. Frequency of cognitive impairment and pulmonary dysfunction was associated with severity of acute COVID-19. Non-hospitalized patients with positive SARS-CoV-2 testing had similar findings than those with negative or no test results.

Conclusions: The CCC experience shows common utilization of multiple specialists by long COVID patients, who harbor frequent neurologic, pulmonary, and cardiologic abnormalities. Differences in post-hospitalization and non-hospitalized groups suggest distinct pathogenic mechanisms of long COVID in these populations.

Introduction:
As of March 23, 2023, over 103 million people in the United States developed confirmed infection with severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), and more than 1.1 million have died from coronavirus disease 2019 (COVID-19)[1]. Many patients who are infected with SARS-CoV-2 continue to have symptoms more than four weeks after acute infection[2]. Termed "Long COVID" or "Post-Acute Sequelae of SARS-COV-2 infection" (PASC)[3,4] this syndrome may include shortness of breath, palpitations, brain fog, and fatigue, among other symptoms[2,5,6], and may persist for more than two years[7,8]. Patients suffering from the protean manifestations of long COVID need multispecialty care[9].

The incidence of long COVID is remains uncertain, with estimates ranging from 30 to 50%[10]. The wide variation in reported incidence reflects different definitions used for long COVID over the course of the pandemic; the Center for Disease Control (CDC) defines long COVID as new or persistent symptoms at least 4 weeks after COVID-19 diagnosis[4], whereas the World Health Organization (WHO) defines long COVID as symptoms lasting over 3 months[11]. Despite this variability, the Government Accountability Agency estimated in March 2022 that up to 23 million Americans suffered from long COVID[12].

To care for these patients, multidisciplinary clinics have been established to facilitate coordination of care between specialties. However, the approach to caring for patients with PASC varies widely among institutions and providers[13]. Little is known about the characteristics and outcomes of patients who seek care at post-COVID centers[14].

The Northwestern Medicine Comprehensive COVID-19 Center (CCC) in Chicago was among the first multidisciplinary clinics dedicated to long COVID care in the United States (US). Here, we describe the history and structure of the CCC, and characterize the demographic and clinical presentation of long COVID patients during the first 21 months of clinic operations.

Methods:
This retrospective cohort study focuses on patients seen at the CCC from May 9, 2020 to February 9, 2022. The cohort was identified using the electronic medical record and assessed for accuracy and completeness by each specialty. Manual chart review was performed for patients with missing information. This study was approved by the institutional review board at Northwestern University (STU00215267). A waiver of informed consent was granted by the IRB due to the retrospective nature of the study.

Since trends in diagnostic testing and results are less informative in clinics with fewer than 100 patient visits, we decided to report results of testing by the three most commonly visited specialties of the CCC: neurology, pulmonology, and cardiology.

Study Setting
Physicians began seeing patients in a dedicated long COVID clinic in May 2020 within the department of neurology. In September 2020, the clinic expanded to include physicians within the departments of medicine, surgery, dermatology, and psychiatry. Providers from twelve specialties saw patients within the CCC, including neurology, pulmonology, cardiology, otolaryngology, gastroenterology , infectious disease, endocrinology, nephrology, hematology, dermatology, psychiatry and rheumatology. Patients were scheduled through physician referral, hospital discharge care coordination, and self-referral (**Figure 1**). To provide full access to patients in pandemic times, physician referral, a positive SARS-CoV-2 test, or proof of insurance were not required to make an appointment at the CCC, in person or through

telehealth. Adult patients with persistent symptoms at least 30 days after confirmed or suspected SARS-CoV-2 infection who were referred to or requested an appointment at the CCC were screened by trained clinic staff. Patients who met clinical criteria had their appointment scheduled with the appropriate specialist(s). Further specialty referrals within the CCC could be arranged at the discretion of the treating provider.

The CCC was established as a pragmatic response to provide care for large numbers of post-COVID patients in early phases of the pandemic. Therefore, strict clinical protocols with standardized testing for each patient was not part of the care pathways of the center. All diagnostic tests and therapies were directed by the treating physician based on their clinical history and physical exam.

The CCC was established before consensus definitions of long COVID were published[4,11], so it was not known when patients should be evaluated after their acute infection. In the absence of published guidelines, CCC providers generated a protocol wherein patients were evaluated at least 30 days after onset of symptoms. This protocol is concordant with the CDC definition of long COVID,[4] but differs from the WHO 3 month definition that was published subsequently.[11]

Center Procedures – Neurology

Clinical criteria for appointment to the neurology clinic included individuals with confirmed diagnosis of SARS-CoV-2 infection or carrying a diagnosis of COVID-19 presenting with brain fog, cognitive problems, confusion, headache, decreased sense of smell and taste, weakness, numbness, muscle pain and loss of consciousness. People with no diagnosis of COVID-19 but worried they have been exposed to SARS-CoV-2 or having neurologic symptoms listed above were evaluated as well. Prior to the office visit, patients were asked to answer the validated patient reported outcome measure information system (PROMIS) questionnaires for self-perceived quality of life in domains of cognitive function (PROMIS Cognitive function: Computer-Adaptive Test v2.0), fatigue, sleep disturbance, anxiety and depression (PROMIS Fatigue, sleep, anxiety, depression: Computer-Adaptive Test v1.0). Formal cognitive testing of in-person patients was performed using the NIH Toolbox v2.1 tests for processing speed (pattern comparison processing speed test), attention and executive memory (inhibitory control and attention test), executive function (dimensional change card sort test) and working memory (list sorting working memory test) as previously described[6]. Both PROMIS and NIH Toolbox results are expressed in T scores with NIH Toolbox results adjusted for age, education, gender, race/ethnicity as previously described[6]. Moderate impairment was defined as PROMIS or NIH Toolbox results abnormal by >1 standard deviation, and severe impairment was defined as PROMIS or NIH Toolbox results abnormal by >2 standard deviations.

Center Procedures - Pulmonology

Clinical criteria for referral to the pulmonology clinic within CCC included shortness of breath, chronic cough, hypoxemia, or abnormal chest imaging findings. There is a lack of consensus regarding the appropriate testing algorithm for patients with respiratory long COVID. Our approach, described elsewhere,[15] recognizes the lack of sensitivity of chest plain radiographs after COVID-19 infection in detection of lung injury.[16] Chest computed tomography scans (CTs) were pursued in patients with persistent symptoms and/or abnormal pulmonary function tests (PFTs).

PFTs performed at least 30 days after COVID-19 infection were identified either by electronic query through the Northwestern Enterprise Data Warehouse or direct chart review. The percent of predicted forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), FEV1/FVC ratio, total lung capacity (TLC), and diffusing capacity of lung for carbon monoxide (DLCO) were recorded. FEV1, FVC,

TLC, and diffusing capacity were considered abnormal if less than 80% predicted and FEV1/FVC ratio was considered abnormal if less than 70% predicted.

Finalized radiologist reports of CT scans of the chest from patients seen by pulmonology, obtained at least 30 days after COVID-19 diagnosis date, were reviewed by a board-certified pulmonologist. Non-contrast CT scans of the chest, high resolution CT scans, and CT scans using intravenous contrast were all included as some patients underwent CT imaging before evaluation within the CCC. Reports of findings of fibrosis (focal or diffuse), consolidation, opacities (most were ground glass, but "opacity" not specified further was included), and air-trapping were recorded. "Fibrosis" was either mentioned specifically in the radiology report or based on surrogate terminology ("honeycombing," "subpleural reticulation," "traction bronchiectasis" or "traction bronchiolectasis," and/or "scarring"). Specific use of the term "organizing pneumonia" was documented. Severity of the abnormalities was not quantified.

Center Procedures - Cardiology

Clinical criteria for referral to the cardiology clinic within CCC included chest pain, shortness of breath, dizziness or lightheadedness, palpitations, swelling of the legs or belly, trouble sleeping because of shortness of breath, or exercise intolerance. All patients referred to cardiology underwent electrocardiogram at time of visit. Echocardiography, cardiac magnetic resonance imaging (CMR), and rhythm monitoring were ordered at the request of the ordering physician.

Study Design

Determination of COVID-19 Diagnosis

Positive SARS-CoV-2 laboratory testing (nasopharyngeal (NP) RT-PCR, NP antigen, or serology) is not a requirement for evaluation at our center, but test results, when available, were recorded. As reliable vaccination data was not available across the cohort, serology data was adjudicated as follows: anti-SARS-CoV-2 nucleocapsid antibody reactivity was counted as indicative of previous COVID-19 infection and a positive anti-SARS-CoV-2 spike antibody or total antibody reactivity were only considered as indicative of previous infection if obtained before January 1, 2021, when COVID-19 vaccines became available. Therefore, serologic testing was considered definitive if any serologic test was positive before January 1, 2021 or if an anti-nucleocapsid serology was positive on or after January 1, 2021. Severity of illness was assessed by hospitalization for acute COVID-19 infection and mechanical ventilation due to COVID-19 pneumonia-related respiratory failure. If a positive antigen or PCR test was not documented, symptom onset date was used as a surrogate. Suspected SARS-CoV-2 infection was determined according COVID-19 IDSA guidelines.[16]

Statistical Analysis

To assess the impact of severity of acute COVID-19 infection on long COVID outcomes, the CCC cohort was analyzed in two groups: post-hospitalization patients (with or without intubation for respiratory failure), and non-hospitalized patients (with or without SARS-CoV-2 positive test)

Cohort characteristics were described using median +/- inter-quartile range (IQR) for continuous variables and sample size and percentage for categorical variables. Normal distribution was not assumed for reported parameters; therefore mean and standard deviation were not routinely calculated. Statistical significance was calculated across all groups with a two-way ANOVA test. Hypothesis testing for dichotomous variables was performed with chi squared test ($n \geq 50$) or fisher's exact test ($n < 50$). Hypothesis testing for continuous variables was performed with Mann-Whitney U test.

Results:
Between May 9, 2020 and February 9, 2022, 1802 patients were evaluated by CCC providers. Complete demographic data are presented in **Table 1.**

Of 1802 patients, 452 (25.1 %) non-hospitalized patients did not have laboratory evidence of SARS-CoV-2 infection. Among these, 230 (50.9%) had negative SARS-CoV-2 nasal RT-PCR or antigen testing, 151 (33.4%) were not tested during their acute COVID-19 symptoms, and 71 (15.7%) had no documentation of testing. In addition, of these 452 patients, 193 (42.7%) had negative serologic testing, 43 (9.5%) were anti-spike antibody positive after January 1, 2021 and 216 (47.8%) never underwent serologic testing.

There was no time difference from symptom onset to first clinic visit between intubated and non-intubated post-hospitalization patients, but non-hospitalized patients who were SARS-CoV-2-negative or not tested presented 3.6 months later to the CCC than those with documented COVID-19 diagnosis **(Table 1)**.

Specialty utilization

Patients were evaluated in a total of 2361 initial specialty visits. The most utilized specialties within the CCC were neurology, pulmonology, and cardiology with 1151 (48.8%), 591 (25%) and 284 (12%) new patients visits, respectively, comprising 85.8% of all visits **(Figure 2)**. The mean number of specialty clinics visited by CCC patients was 1.3 (range 1-6), and multiple clinic consultations accounted for 405 (17.2%) visits. The three clinics reported on in detail in this study were the most commonly overlapping specialties: 166 (9.2%) patients saw both pulmonary and neurology, 133 (7.4%) patients saw both pulmonary and cardiology, and 90 (5.0%) patients saw both neurology and cardiology.

Neurology Clinic

Quality of life (QoL) and cognitive test results of Neurology patients are shown in **Table 2**.

Symptoms in patients presenting to the neurology CCC have been described previously[6]. The majority of post-hospitalization and non-hospitalized patients experienced moderate impairment in QoL in domains of cognition, fatigue, sleep disturbance, anxiety, and depression. Post-hospitalization patients who required intubation were less likely to report moderate or severe impairment in domains of cognition and fatigue than hospitalized patients who were not intubated. Conversely, among non-hospitalized patients who experienced moderate or severe impairment of QoL, there were no significant differences in the quality of life measures in areas of cognition, fatigue, sleep, anxiety, and depression, and in the cognitive test results of processing speed, attention, executive function, or working memory between non-hospitalized patients with positive SARS-CoV-2 test compared to those who did not have a positive test. However, patients whose COVID-19 diagnosis was not confirmed by SARS-CoV-2 test more frequently experienced severe fatigue than those with a positive SARS-CoV-2 test.

More than half of previously hospitalized patients showed moderate or severe impairment, and close to one-third showed severe impairment on at least one standardized cognitive test. However, there was no difference based on intubation status. This suggests that hospitalized patients who were intubated for severe COVID-19 disease may have less insight into their cognitive dysfunction than those who did not require intubation. Conversely, close to half non-hospitalized patients showed moderate or severe impairment in at least one cognitive test, regardless of their SARS-CoV-2 test results. However, those with unconfirmed COVID-19 diagnosis were more likely to show severe impairment in at least one cognitive test. Comparison of cognitive test results between post-hospitalization and non-hospitalized

groups showed significant differences in processing speed test, which was more frequently moderately or severely impaired in the post-hospitalization patients compared to non-hospitalized patients.

These results demonstrate that a median of 8.0 months from symptoms onset, most previously hospitalized and non-hospitalized patients experience impaired QoL as well as cognitive dysfunction.

Pulmonology Clinic

The most common symptoms for presentation to pulmonary clinic were shortness of breath, decreased exercise tolerance, and cough. PFT and chest CT results are shown in **Table 3**. Total lung capacity (TLC), forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and diffusing capacity for carbon monoxide (DLCO) were obtained after COVID-19 infection for 442 patients seen by pulmonologists within the CCC. When stratified by severity of acute illness, significant differences were found across all PFT parameters except the FEV1/FVC ratio. Impairment of TLC, FEV1, FVC, and DLCO correlated significantly with severity of acute illness, consistent with a progressive pattern of restrictive lung disease with diffusion limitation in PASC patients.

The most frequent chest CT abnormalities included pulmonary fibrosis (75.6%) and ground glass opacities (78%) in previously intubated patients. CT abnormalities were more frequent in patients with greater degrees of acute illness severity, except air trapping, which was equally common in all groups. CT abnormalities were also present in the majority (111/150;74%) of non-hospitalized patients, with or without positive SARS-CoV-2 test, including ground glass opacities, fibrosis, and air trapping.

PFTs and chest CT revealed abnormalities in over one-third of patients seen by pulmonology, including those without a history of intubation or severe pneumonia. Persistent non-fibrotic lung injury patterns (e.g., ground glass opacities, organizing pneumonia, consolidation) were seen more than 3 months after acute infection.

Cardiology Clinic

Symptoms and test results for cardiology patients are shown in **Table 4**. Chest pain and palpitations were the most frequent symptoms, but the majority of patients had no evidence of active myo- or pericarditis or clinically significant arrhythmias. Of 59 patients who had CMR, 8 (13.6%) had abnormal findings, including 2 with active myocarditis, 3 with pericarditis, and 3 with evidence of prior myocarditis of undetermined timing. Of those 8 patients, 7 (87.5%) presented with chest pain, 8 (100%) with palpitations, 1 had decreased left ventricular (LV) strain, and 1 had diastolic dysfunction. The median time to CMR from onset of COVID infection was 8.3 months, so while earlier cardiac involvement may have been missed, CMR results did not demonstrate ongoing inflammation in the majority of patients who underwent CMR for cardiovascular symptoms.

Of 198 echocardiograms, one had evidence of confirmed new reduced ejection fraction (EF) (<50%), and one additional patient had left ventricular EF <50% but no prior echo data to confirm an acute change. Neither patient had evidence of myocarditis on CMR. Hospitalized long COVID patients had significantly higher rates of echocardiographic diastolic dysfunction and decreased right ventricular (RV) strain. There was no significant difference in echocardiographic findings based on intubation status among hospitalized patients.

Of 116 rhythm monitors performed, 2 (1.7%) showed clinically significant ventricular arrhythmias (symptomatic non-sustained ventricular tachycardia (NSVT), multiple NSVT runs, sustained ventricular tachycardia (VT), or premature ventricular contraction (PVC) burden >5%) and 1 identifying new atrial fibrillation; 14/116 (12.1%) had an average heart rate of ≥90 bpm which can be consistent with

inappropriate sinus tachycardia. Of the 6 patients that underwent tilt table testing after initial consult, 2 met diagnostic criteria for postural orthostatic tachycardia syndrome (POTS).

Discussion

The disease burden of long COVID continues to grow in the US, with significant implications for both the economy and population health. The Government Accountability Office estimated in March, 2022 that up to 23 million people in the US have been affected by long COVID, pushing one million people out of work[12]. The American Academy of Neurology stated in July 2022 that long COVID had become the third leading neurologic disorder in the US[17].

We report specialty utilization and clinical findings of patients seeking care at a comprehensive multi-disciplinary center for long COVID/PASC. We highlight a wide variety of abnormal neurologic, pulmonary, and cardiac findings, underscoring the need for multidisciplinary care for patients with long COVID. Our CCC intake process was designed to facilitate access for patients with diverse chief complaints. These investments in accessibility promoted a broad national catchment area (close to half of patients were seen by neurology via telehealth from 41 states) and a wide array of illness severity.

Rather than centralizing care within internal medicine[14], the CCC provided a comprehensive approach to patient care in existing specialty clinics, allowing for optimal cross-consultation for an individual patient. While three specialties (neurology, pulmonology, and cardiology) accounted for 85.8% of visits to the CCC, many patients sought care at >1 clinics. This multidisciplinary approach using pre-defined clinical criteria may optimize cost-effectiveness by triaging patients directly to the appropriate specialists. A significant body of work has emerged commenting on interdisciplinary rather than multidisciplinary care for long COVID[18,19]. These studies emphasize the challenges in coordination of care and clarifying appropriate dynamic between specialties in long COVID care[20]. Our center's experience contributes to this body of work by describing a large multidisciplinary clinic and demonstrating the staffing requirements and clinical volume expectations for other centers. It also enables clinical and translational research on the root causes of long COVID as well as establishment of treatment guidelines in this patient population[15,21-25]. Other notable post-acute COVID models use inpatient severity of illness to triage patients to physical rehabilitation.[26]

The Centers for Disease Control has described long COVID as a "wide range of new, returning or ongoing symptoms lasting more than 4 weeks after infection with SARS-CoV-2"[4]. While this definition encompasses the broad range of patients affected by post-COVID sequelae, it does not distinguish between individuals requiring hospitalization for severe COVID-19 pneumonia and those with mild acute infection. While only < $1/5^{th}$ of the neurology and cardiology clinic patients were previously hospitalized, those patients accounted for >$1/3^{rd}$ of the pulmonology clinic visits. Our data show that critically ill, hospitalized, and non-hospitalized patients have distinct neurologic, pulmonary and cardiac manifestations of long COVID, which should be studied and treated differently.

Our results further demonstrate that long COVID patients commonly present with persistent multisystem disorders. Among patients who underwent testing, 85% reported decreased quality of life, 51% had cognitive impairment, 44.9% had alteration of lung function, 83.3% had abnormal CT chest scans, and 12.1% had abnormally elevated heart rates on rhythm monitoring. These findings support the role of many disciplines caring for and evaluating patients with long COVID. In particular, multidisciplinary long COVID clinics can recognize and respond to heterogenous presentations and manifestations of long COVID more quickly than other care models. The possible etiologies of long COVID are still a matter of intense investigation[27]. However, our data clearly shows differences in

outcomes based on acute COVID-19 severity. Indeed, post-hospitalization patients may have sustained permanent damage caused by hypoxemia, cytokine storm, intravascular clotting, and multi-organ failure during the acute phase. Conversely, non-hospitalized patients who only had a mild initial respiratory presentation may suffer from an auto-immune syndrome triggered by viral persistence, as suggested by their younger age and female predominance, since women are more likely than men to develop autoimmune diseases[28]. Immunological studies on well characterized clinical cohorts such as this one may prove very useful to elucidate the pathogenic mechanisms of long COVID in those distinct populations.

Our decision to accept patients without a positive SARS-CoV-2 test was deliberate, and we have previously estimated that approximately 10 million people in the US fall into this category.[29] Briefly, it was motivated by: 1) limitations of nasopharyngeal swab RT-PCR testing for people with mild respiratory symptoms at the beginning of the pandemic; 2) high false-negative RT-PCR rates after day 3 of symptom onset[30]; 3) low sensitivity of the first commercially available anti-Nucleocapsid serology test (Abbott)[31,32]; 4) rapidly decaying anti-Nucleocapsid antibody titers[33-37]; and 5) screening of patients based on Infectious Disease Society of America clinical criteria for COVID-19. In fact, those patients belong to "probable" or "suspected" cases of SARS-CoV-2 infection based on the World Health Organization case definitions, released after the CCC was opened[38].

This sizeable population, which predominantly consisted of females in their forties, has been stigmatized and rejected by medical providers. Seventy percent (45/64) of US post COVID clinics[39] contacted by phone stated that they would not accept those patients[29]. This may explain why they were seen an average of 3.6 months later in our clinics. Our data shows that these patients have objective findings similar to those of non-hospitalized patients with positive SARS-CoV-2 testing and deserve the same investigations and treatment.

Many patients suffer from concurrent "brain fog", chronic fatigue, cardiopulmonary symptoms, and resulting exercise intolerance, which can lead to a vicious cycle of further deconditioning. Our results highlight the multifactorial aspects leading to impaired quality of life experienced by those patients. Although COVID-19 is predominantly a respiratory disease, our data indicate the importance of neurological manifestations of long COVID and the different patterns of cognitive dysfunction based on acute COVID-19 severity. This heterogeneity warrants careful neuro-cognitive evaluation leading to targeted interventions with metacognitive strategy training, that we are currently performing. The fact that half of our patients came in the Neurology clinic in televisits from 41 US states underlines a significantly unmet need for neurologists willing to care for this growing patient population and should inform the need for staffing post-COVID clinics with Neurology providers.

The decreased FEV1, FVC, TLC, and DLCO indicates that restrictive defects with diffusion limitation are common PFT abnormalities in our patients, which is explained by the high proportion of CT scan parenchymal abnormalities also identified. While we expected to find lasting pulmonary damage in patients hospitalized with severe COVID-19 pneumonia, the extent of the radiographic and PFT abnormalities in non-hospitalized patients was surprising. Reduction in total lung capacity, impaired diffusing capacity, and CT scan lung abnormalities were found in about 12%, 30%, and 74% of non-hospitalized patients, respectively, which highlights the important pulmonary disease burden affecting PASC patients despite a mild initial respiratory presentation of COVID-19.

Further, non-fibrotic CT parenchymal abnormalities in both hospitalized and non-hospitalized individuals in our cohort were found long after acute infection (medians of 3.9-8.1 months after COVID-19

diagnosis). This could support the model that proinflammatory circuits between infected macrophages and T-cells drive a prolonged viral lung injury, which may be the reason that organizing pneumonia is frequently reported on chest imaging.[23,40] Our findings underscore the importance of mechanistic investigations into the causes of persistent radiographic abnormalities in long COVID patients. In particular, it is of the utmost importance to identify targetable pathways to support the use of therapeutics such as glucocorticoids to mitigate the onset of fibrotic damage if recognized during earlier, modifiable stages of lung injury.

Sinus tachycardia and exaggerated heart rate response to activity has been demonstrated in long COVID populations and may be responsible for the high rates of palpitation symptoms.[41,42] Sinus tachycardia over 90 bpm was the most frequent rhythm abnormality found in our patients, and other arrythmias were rare. The lack of significant difference echocardiographic findings in hospitalized patients with or without intubation suggest that in RV dysfunction and strain may not be a function of mechanical ventilation alone and may reflect underlying micro and macro thromboembolic phenomena or direct myocardial injury present in sever COVID-19 cases.[43]

COVID-19 is expected to remain endemic in the US.[44] With increasing vaccination rates and the emergence of new SARS-CoV-2 variants, it is likely that the phenotypes of long COVID will continue to change over time. One study of more than 13 million people showed that vaccination and boosting has only decreased the risk of developing long COVID by about 15%[45]. The heterogeneity of the symptoms described in this study highlights the crucial need for continued health system investment and support of multidisciplinary COVID centers. Those centers may also participate in studies of the evolution of long COVID symptoms, providing additional value to researchers.

Strengths of this study include cohort size, multidisciplinary experience, and inclusion of patients over the entire spectrum of COVID-19 disease severity from a broad national catchment area. This study also has several limitations. The predominance of neurology clinic utilization may be different than other medical centers where post-COVID clinics are staffed by internal medicine physicians and do not have a Neurology clinic dedicated to the care of long COVID patients. As with any study performed in an outpatient setting on any disease, our cohort consists of self-selected individuals who sought care at the CCC. However, the centralized scheduling for the 12 specialty clinics of the CCC as well as our policy allowing in-person or telehealth visits without physician referral was specifically designed to improve access and avoid referral bias. Therefore, our study is representative of the population of Long COVID patients who seek care at post-COVID clinics in the US. Finally, our study is not a prospective health services research study on a well-known disease. Our center emerged as a pragmatic solution to provide care for a large population of patients presenting with a novel multisystem syndrome despite the limitations on health systems during Phase 1 of the pandemic.[46] Our real-world data will inform physicians and health systems about the complex manifestations and health care focused on the unique and heterogeneous needs of long COVID patients (Phase 2).[46]

Conclusion

There is a great need for multidisciplinary clinics to form the backbone of the response to long COVID[47,48]. This study is the first to describe the operational structure and diagnostic impact of such a multidisciplinary effort, and could be an example for use in future viral outbreaks[49,50].

Long COVID affects 10-30%[2,51,52] of SARS-CoV-2-infected individuals, depending on variant and severity of acute illness. This “pandemic within the pandemic” continues despite SARS-CoV-2 vaccination and

boosting. Patients present with multisystemic symptoms requiring specialty care and harbor a broad range of neurologic, pulmonary and cardiologic abnormalities, warranting targeted interventions. Differences between the post-hospitalization and non-hospitalized groups suggest distinct pathogenic mechanisms and highlight the need for further research to determine the root cause of long COVID in those populations.

Acknowledgements

This work was supported in part by the Northwestern Medicine Enterprise Data Warehouse.

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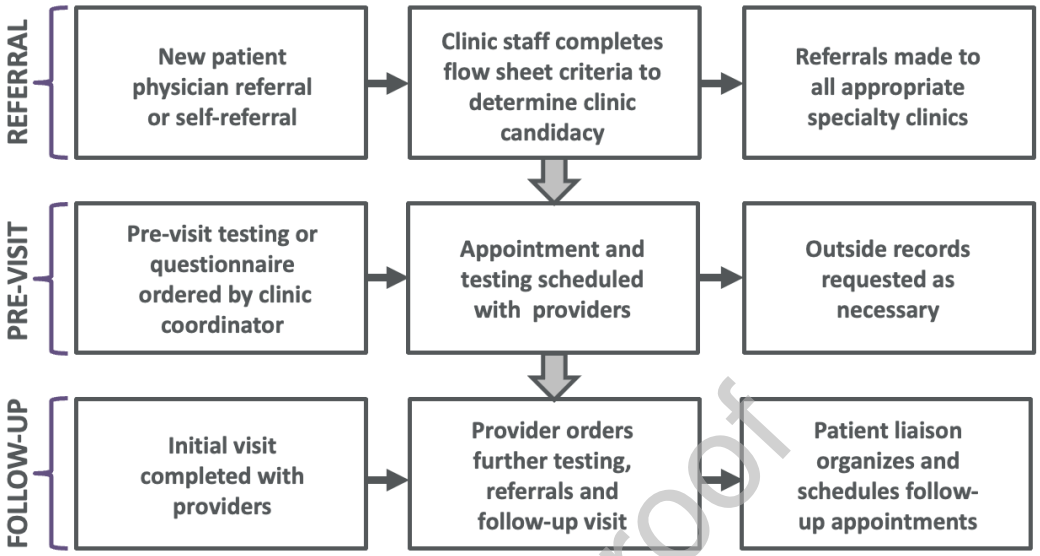
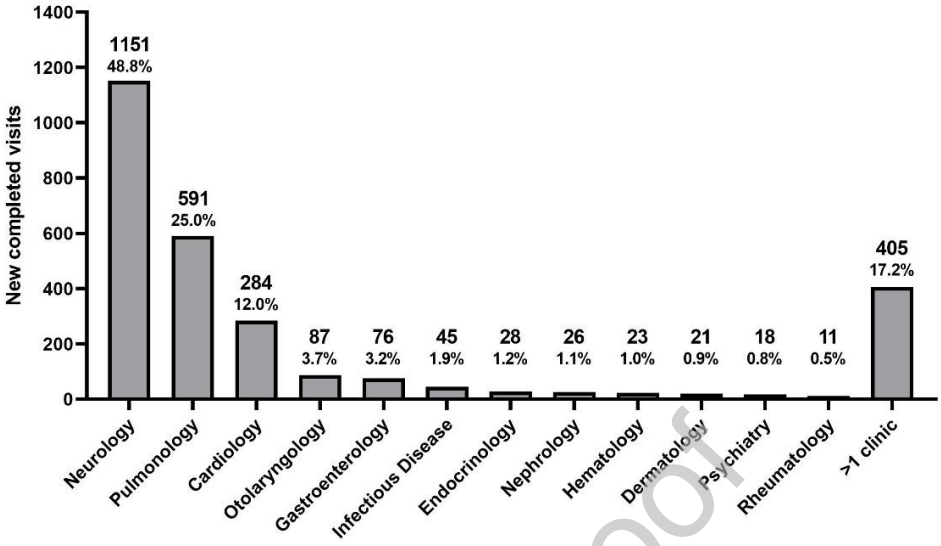
Figure 1: CCC scheduling process map



CCC Scheduling Process Map. New patients were screened by clinic staff and completed pre-visit questionnaires prior to their initial visit evaluation in specialty clinic, followed by additional testing and referrals.

Figure 2: Specialty Utilization



Specialty utilization by a total of 1802 patients evaluated at the Comprehensive COVID Center (CCC) during the first 21 months in a total of 2361 initial visits in 12 specialty clinics. The mean number of specialty clinics visited by CCC patients was 1.3 (range 1-6) and multiple clinic consultations accounted for 405 visits.

Table 1: Demographic data

Statistical testing: Hypothesis testing for dichotomous variables was performed with chi squared test. Hypothesis testing for continuous variables was performed with Mann-Whitney U test.

Abbreviations: : [a]Hosp: previous hospitalization for COVID-19. [b]IQR: Inter-quartile range. [c]BMI: Body mass index

	Hosp[a] intubated COVID-19 n=84	Hosp[a] /not intubated COVID-19 n=266	*p* Hosp[a]	Non-hosp[a] COVID-19 n=1000	Non-hosp[a] SARS-CoV-2 neg/no test n=452	*p* Non-hosp[a]	Overall n=1802	*p* hosp[a] vs. non-hosp[a]
Demographics	n /total (%) or median (IQR[b])							
Female sex	26 (31.0)	147 (55.3)	0.27	673 (67.3)	318 (70.4)	**0.0002**	1164 (64.6)	**0.0002**
BMI[c]	31.3 (26.7 – 36.5)	31.0 (27.0 – 37.0	0.91	27.9 (23.7 – 32.0)	26.0 (22.3 – 30.5)	0.008	28.3 (24.0 – 33.4)	**<0.0001**
Age at first clinic visit (years)	56.0 (49.0 – 66.0)	56.0 (48.0 – 66.0)	0.89	45.0 (35.0 – 55.3)	43.0 (34.0 – 54.0)	0.15	47 (36-57.8)	**<0.0001**
Acute COVID to first clinic visit (months)	7.1 (3.7 – 9.7)	5.6 (2.8 – 9.3)	0.13	6.1 (3.7 – 9.9)	9.7 (6.3 – 15.1)	**<0.0001**	8.0 (3.9 – 11.1)	**<0.0001**
Race	n /total (%)							
White	41 (48.8)	161 (60.5)	0.08	734 (73.4)	352 (77.9)	0.08	1288 (71.5)	**<0.0001**
Black or African American	19 (22.6)	53 (19.9)	0.71	89 (8.9)	27 (6.0)	0.07	188 (10.4)	**<0.0001**
Asian	3 (3.6)	7 (2.6)	0.94	41 (4.2)	14 (3.1)	0.44	65 (3.6)	0.50
American Indian or Alaska Native	1 (1.2)	1 (0.4)	0.97	2 (0.2)	1 (0.2)	1	5 (0.3)	0.55
Native	0 (0)	1 (0.4)	1	1 (0.1)	2 (0.4)	0.48	4 (0.2)	1

Hawaiian or Pacific Islander								
Other	20 (23.8)	43 (16.2)	0.15	133 (13.3)	56 (12.4)	0.69	252 (14.0)	**0.02**
Ethnicity	n /total (%)							
Hispanic or Latino	25 (29.8)	48 (18.0)	**0.03**	128 (12.8)	36 (8.0)	**0.009**	237 (13.2)	**<0.0001**
Not Hispanic or Latino	56 (66.7)	208 (78.2)	**0.05**	821 (82.1)	385 (85.2)	0.17	1470(81.6)	**0.001**
Other	3 (3.6)	10 (3.8)	1	51 (5.1)	31 (6.9)	0.22	95 (5.3)	0.19

Table 2: Quality of life and cognitive assessment in neurology patients

	Hosp[a] intubated COVID-19 n=31	Hosp[a] /not intubated COVID-19 n=113	*p* Hosp[a]	Non-hosp[a] COVID-19 n=705	Non-hosp[a] SARS-CoV-2 neg/no test n=302	*p* Non-hosp[a]	Overall n=1151	*p* Hosp[a] vs Non-hosp[a]
Time from onset (mo, median [IQR])	8.8 [5.7-13.0]	7.7 [4.6-11.3]	0.12	7.3 [4.6-11.1]	10.2 [6.7-16.0]	**<0.0001**	8.0 [5.1-12.1]	0.33
Visit type, n (%)			0.69			**<0.0001**		0.37
In-person	16 (52)	63 (56)		385 (55)	124 (41)		588 (51)	
Televisit	15 (48)	50 (44)		320 (45)	178 (59)		563 (49)	
PROMIS	Moderate or severe impairment[b]: n abnormal/n tested							
Cognition	8/22 (36)	58/83 (70)	**0.006**	340/564 (60)	159/235 (68)	0.05	565/904 (63)	0.83
Fatigue	6/22 (27)	57/84 (68)	**0.001**	346/567 (61)	159/236 (67)	0.09	568/909 (62)	0.52
Sleep disturbance	3/18 (17)	19/68 (28)	0.54	166/509 (33)	43/158 (27)	0.24	231/753 (31)	0.32
Anxiety	7/18 (39)	40/67 (60)	0.18	261/511 (51)	80/158 (51)	0.93	388/754 (51)	0.49
Depression	2/18 (11)	19/66 (29)	0.22	132/507 (26)	46/159 (29)	0.47	199/750 (27)	0.79
Any PROMIS	12/22 (55)	74/84 (88)	**0.001**	457/573 (80)	199/237 (84)	0.17	742/916 (81)	1
PROMIS	Severe impairment[c]: n abnormal/n tested							
Cognition	0/22 (0)	15/83 (18)	**0.04**	76/564 (13)	41/235 (17)	0.15	132/904 (15)	1
Fatigue	1/22 (5)	20/84 (24)	0.07	106/567 (19)	67/236 (28)	**0.003**	194/909 (21)	0.80
Sleep disturbance	2/18 (11)	2/68 (3)	0.19	24/509 (5)	8/158 (5)	0.83	36/753 (48)	1
Anxiety	0/18 (0)	8/67 (12)	0.19	45/511 (9)	20/158 (13)	0.17	73/754 (10)	1
Depression	0/18 (0)	1/66 (2)	1	13/507 (3)	6/159 (4)	0.41	20/750 (3)	0.72
Any PROMIS	3/22 (14)	34/84 (40)	**0.02**	180/573 (31)	97/237 (41)	**0.01**	314/916 (34)	0.91
NIH Toolbox	Moderate or severe impairment[b]: n abnormal/n tested							
Processing speed	9/18 (50)	34/68 (50)	1	103/366 (28)	32/101 (32)	0.54	178/553 (32)	**0.0002**
Attention	8/18 (44)	28/68 (41)	0.8	115/366 (31)	32/101 (32)	1	183/553 (33)	0.06
Executive function	3/18 (17)	23/68 (34)	0.25	99/366 (27)	32/101 (32)	0.38	157/553 (28)	0.70
Working memory	2/18 (11)	17/68 (25)	0.34	66/366 (18)	16/101 (16)	0.66	101/553 (18)	0.36

Any Toolbox	11/18 (61)	46/68 (68)	0.59	178/366 (49)	49/101 (49)	1	284/553 (51)	**0.003**
NIH Toolbox	Severe impairment[c]: n abnormal/n tested							
Processing speed	3/18 (17)	19/68 (28)	0.54	34/366 (9)	18/101 (18)	**0.02**	74/553 (13)	**0.0008**
Attention	2/18 (11)	8/68 (12)	1	39/366 (11)	17/101 (17)	0.12	66/553 (12)	1
Executive function	0/18 (0)	9/68 (13)	0.19	34/366 (9)	17/101 (17)	0.05	60/553 (11)	1
Working memory	0/18 (0)	1/68 (1)	1	7/366 (2)	2/101 (2)	1	10/553 (2)	1
Any Toolbox	5/18 (28)	21/68 (31)	1	70/366 (19)	29/101 (29)	**0.04**	125/553 (23)	0.07

[a]Hosp: previous hospitalization for COVID-19

[b]For moderate and severe impairment, PROMIS and NIH Toolbox tests are abnormal by >1 SD

[c]For severe impairment, PROMIS and NIH Toolbox tests are abnormal by >2 SD

Table 3: Pulmonary function testing and chest CT results in pulmonary patients.

Statistical testing: Hypothesis testing for dichotomous variables was performed with chi squared test (n≥50) or Fisher's exact test (n<50). Hypothesis testing for continuous variables was performed with Mann-Whitney U test.

Abbreviations: [a]Hosp: previous hospitalization for COVID-19. [b]PFT: Pulmonary function test. [c]FEV1: forced expiratory volume in one second. [d]FVC: forced vital capacity. [e]TLC: total lung capacity. [f]DLCO: diffusing capacity of the lung for carbon monoxide. [g]CT: computed tomography. [h]IQR: Inter-quartile range

	Hosp[a] intubated COVID-19 n=58	Hosp[a] /not intubated COVID-19 n=153	*p* Hosp[a]	Non-hosp[a] COVID-19 n=275	Non-hosp[a] SARS-CoV-2 neg/no test n=105	*p* Non-hosp[a]	Overall n=591	*p* hosp[a] vs. non-hosp[a]
PFT[b] findings	n abnormal/n tested (%) or median (IQR[h])							
Onset to PFT[b] (months)	6.5 (4.3 – 9.0)	5.8 (3.3 – 10.4)	0.70	6.6 (3.8 – 10.3)	12.7 (6.2 – 16.7)	**<0.0001**	7.3 (4.1 – 11.4)	**0.006**
FEV1[c]	27/39 (69.2)	41/114 (36.0)	**0.0006**	43/211 (20.4)	17/78 (21.8)	0.92	128/442 (30.0)	**<0.0001**
FVC[d]	27/39 (69.2)	44/114 (38.6)	**0.002**	37/211 (17.5)	14/78 (17.9)	1	122/442 (27.6)	**<0.0001**
Ratio	2/39 (5.1)	12/114 (10.5)	0.49	17/211 (8.1)	10/78 (12.8)	0.31	41/442 (9.3)	1
TLC[e]	29/38 (76.3)	42/110 (38.1)	**<0.001**	26/208 (12.5)	9/74 (12.2)	1	106/430 (24.7)	**<0.0001**
DLCO[f]	35/39 (90.0)	74/112 (66.1)	**0.008**	64/209 (30.6)	22/74 (29.7)	1	195/434 (44.9)	**<0.0001**
CT[g] findings	n abnormal/n tested (%) or median (IQR[h])							
Onset to CT (months)	4.5 (2.0 – 7.4)	3.9 (2.1 – 6.9)	0.61	4.6 (2.8 – 9.4)	8.1 (4.2 – 14.8)	**0.001**	4.6 (2.5 – 8.1)	**0.0002**

Fibrosis	31/41 (75.6)	45/108 (41.7)	**0.0004**	14/109 (12.8)	4/41 (9.8)	0.81	94/299 (31.4)	**<0.0001**
Consolidation	9/41 (22.0)	8/108 (7.4)	**0.03**	3/109 (2.8)	2/41 (4.9)	0.89	22/299 (7.4)	**0.01**
Ground glass opacities	32/41 (78.0)	70/108 (65.0)	0.18	22/109 (20.2)	10/41 (24.4)	0.74	134/299 (44.8)	**<0.0001**
Organizing pneumonia	9/41 (22.0)	11/108 (10.2)	0.11	5/109 (4.6)	3/41 (7.3)	0.80	28/299 (9.4)	**0.03**
Air trapping	6/41 (14.6)	14/108 (13.0)	1	21/109 (19.3)	6/41 (14.6)	0.68	47/299 (15.7)	0.35
None of the above	1/41 (2.4)	10/108 (9.3)	0.28	26/109 (23.9)	13/41 (31.7)	0.44	50/299 (16.7)	**0.0001**

Table 4: Symptoms and test results in cardiology patients.

Statistical testing: Hypothesis testing for dichotomous variables was performed with chi squared test (n≥50) or Fisher's exact test (n<50). Hypothesis testing for continuous variables was performed with Mann-Whitney U test.

Abbreviations: [a]Hosp: previous hospitalization for COVID-19. [b]Echo: echocardiogram. [c]LVEF: Left ventricular ejection fraction. [d]LV: left ventricle. [e]RV: right ventricle. [f]TAPSE: tricuspid annular plane systolic excursion. [g]cMRI: cardiac magnetic resonance imaging. [h]IQR: Inter-quartile range. [i]VT: Ventricular tachycardia. [j]BPM: beats per minute. [j]POTS: Postural orthostatic tachycardia syndrome.

	Hosp[a] intubated COVID-19 n=14	Hosp[a] /not intubated COVID-19 n=30	*p* Hosp[a]	Non-hosp[a] COVID-19 n=179	Non-hosp[a] SARS-CoV-2 neg/no test n=61	*p* Non-hosp[a]	Overall n=284	*p* hosp[a] vs. non-hosp[a]
Symptoms on presentation	n abnormal/n tested (%) or median (IQR[h])							
Chest pain	4/14 (28.6)	20/30 (66.7)	**0.03**	116/179 (64.8)	34/61 (55.7)	0.27	174/284 (61.3)	0.41
Shortness of breath	8/14 (57.2)	23/30 (76.7)	0.29	110/179 (61.5)	41/61 (67.2)	0.52	182/284 (64.1)	0.43
Palpitations	3/14 (21.4)	16/30 (53.3)	0.06	124/179 (69.3)	45/61 (73.8)	0.62	188/284 (66.2)	**0.0009**
Other	5/14 (35.7)	24/30 (80.0)	**0.007**	154/179 (86.0)	46/61 (75.4)	0.09	229/284 (80.6)	**0.01**
Echo[b] Findings	n abnormal/n tested (%) or median (IQR[h])							
Onset to echo[b] (months)	7.7 (3.3 – 9.7)	4.9 (3.0 – 8.2)	0.58	4.4 (2.8 – 8.5)	10.5 (4.8 – 14.5)	**0.0001**	5.2 (3.0 – 10.0)	0.95
LVEF[c] <50	0/11 (0)	0/20 (0)		1/128 (0.8)	1/37 (2.7)	0.93	2/194 (1.0)	1
Diastolic dysfunction	7/12 (58.3)	9/20 (45.0)	0.72	19/129 (14.7)	4/36 (11.1)	0.78	39/197 (19.8)	**<0.0001**
LV[d] strain (<-17%)	2/7 (28.6)	1/7 (14.3)	1	7/68 (10.3)	1/14 (7.1)	1	11/96 (11.5)	0.42
RV[e] strain (<-20%)	3/6 (50.0)	1/3 (33.3)	1	2/30 (6.7)	0/6 (0)	1	6/45 (13.3)	**0.01**
Low TAPSE[f] (<17)	0/10 (0)	0/20 (0)		7/119 (5.9)	3/35 (8.6)	0.86	10/144 (6.9)	0.32
RV[e] dilation or dysfunction present	3/12 (25.0)	3/20 (15.0)	0.65	7/129 (5.4)	2/36 (5.6)	1	15/197 (7.6)	**0.03**
cMRI[g] Findings	n abnormal/n tested (%) or median (IQR[h])							

Onset to cMRI[g] (months)	12.0 (9.0 – 12.1)	8.7 (5.4 – 10.6)	0.57	6.0 (4.0 – 10.8)	17.6 (15.2 – 19.4)	**0.0007**	8.3 (4.5 – 12.3)	0.83
cMRI[g] myocarditis/ pericarditis	0/3	1/9 (11.1)	1	6/37 (16.2)	1/9 (11.1)	1	8/59 (13.6)	0.81
Rhythm Monitor Findings	n abnormal/n tested (%) or median (IQR[h])							
Onset to Rhythm Monitor (months)	10.7 (8.5 – 15.4)	6.8 (3.3 – 8.9)	0.20	4.6 (3.1 – 8.7)	9.9 (6.5 – 13.4)	**0.0**01	5.8 (3.4 – 11.0)	0.72
Non-sustained VT[i]	0/4 (0)	1/13 (7.7)	1	1/71 (1.4)	0/28 (0)	1	2/116 (1.7)	0.27
Atrial Fibrillation or Flutter	0/4 (0)	1/13 (7.7)	1	0/71 (0)	0/28 (0)		1/116 (0.9)	0.15
Average heart rate over 90 bpm[i]	2/4 (50.0)	4/13 (30.8)	0.58	6/71 (8.5)	2/28 (7.1)	1	14/116 (12.1)	**0.005**
Tilt Table Findings	n abnormal/n tested (%) or median (IQR[h])							
Onset to Tilt Table Test (months)				9.8 (4.5 – 15.1)	13.2 (13.2 – 13.2)	1	11.5 (5.9 – 14.6)	
POTS[j]				2/5	0/1	0.73	2/6 (33.3)	

Clinical Significance

- Multidisciplinary centers efficiently provide access to specialty care for the broad range of organ systems involved in long COVID.
- Neurology, pulmonary, and cardiology are the most commonly utilized specialties in an established multidisciplinary center.
- When long COVID patients receive appropriate specialty care, abnormal diagnostic test results are common, even among patients not hospitalized for acute infection.

Funding: Dr. Joseph Bailey's work on this project is supported, in part, by NIH/NHLBI 5T32HL076139 and NIH/NHLBI UL1TR001422.

Conflicts of Interest: The authors report no conflicts of interest.

Authorship: All authors have read the manuscript and meet the criteria for authorship. Authors will sign a statement attesting authorship, disclosing all potential conflicts of interest, and releasing the copyright should the manuscript be accepted for publication.